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REVIEW

# Breast-Conserving Treatment: Controversies and Consensus

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Although breast-conserving therapy (BCT) is an accepted alternative for the treatment of breast cancer, numerous controversies surround the selection criteria and the treatment details. A review of the literature revealed that patient selection is of critical importance. However, there is disagreement over the relative importance of some of the criteria for patient selection. A wide excision is preferable to a less complete excision (tumorectomy) or a more radical excision (quadrantectomy). Accurate assessment of surgical margins is important. The risk of local recurrence may be diminished if a re-excision is performed to obtain tumor-free margins. However, the suitability and practicality of the techniques used to assess the resection margins have been questioned. Radiotherapy is an integral part of BCT. Surgery alone remains an investigational approach. Axillary dissection remains a reliable method of assessing nodal status and treating regional disease. © 1996 Wiley-Liss, Inc.

KEY WORDS: axillary dissection, breast-conserving therapy, patient selection, radiation

## INTRODUCTION

Breast-conserving therapy (BCT) is the accepted treatment for most women with clinical stage I or II invasive breast cancer [1]. This mode of therapy may be defined as a combination of conservative surgery for resection of the primary tumor with or without surgical staging the axilla, followed by radiotherapy for the eradication of residual microscopic disease in the breast. There is increasing support for the use of this approach [2–4]. The goal of this treatment is to provide satisfactory cosmetic results without compromising local tumor control or survival compared with modified radical mastectomy. However, it is often difficult to satisfy all three objectives in the same patient. It would be a mistake to overlook the second or third objective in order to satisfy the first. The penalty for poor judgment in this type of combination therapy is a relatively high incidence of local recurrence [5]. The higher local recurrence rates results in psychological morbidity for the patient [6] and mandate a longer follow-up. In addition, conservative therapy may, in some cases, lead to aesthetically unacceptable results. Therefore, numerous controversies remain concerning optimal patient selection, and the details of treatment [7,8].

We reviewed the available data regarding the patient selection for BCT, the risk factors for local recurrence, the optimal extent of resection for the primary tumor, the assessment of surgical margins, the indications and extent of axillary dissection, and the indications for radiation after surgical resection.

## PATIENT SELECTION FOR BREAST-CONSERVING TREATMENT

The following absolute and relative contraindications have been proposed [9]. The absolute contraindications are (1) pregnancy in the first or second trimester; (2) two

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or more gross lesions in different quadrants, or diffuse microcalcifications on mammography; and (3) a history of prior radiotherapy to the area, especially in patients with a prior history of Hodgkin's disease. The relative contraindications are (1) a history of collagen vascular disease; (2) a large tumor in relation to the breast size; (3) large, pendulous breasts; and (4) centrally located tumors. Patient selection for BCT is based on the ability to resect the primary tumor without causing major cosmetic deformities and the ability to minimize the likelihood of breast recurrence. However, there is disagreement over the relative importance of the various criteria. Although some institutions restrict BCT to patients with small tumors (≤2.5 cm) [10–12], BCT should not be limited to patients with small tumors. For tumors ≤5 cm, the likelihood of residual cancer is not dependent on tumor size [13,14], which is consistent with the relative lack of significance of tumor size as a risk factor for local recurrence after BCT [15–17]. Patients are considered candidates for BCT if excision of the tumor can be performed without a resultant major cosmetic deformity. This is based on the relative size of tumor and the breast and on the location of the tumor. When tumors are very small, it may be possible to do relatively wide excisions without causing a substantial deformity of the breast. Minor degrees of breast deformity are corrected by transposition of local flaps, wide undermining, and cornization of the residual breast tissue [18-20]. However, when the tumor is large or the breasts are small, it may be difficult to correct the breast deformity using such minor procedures. Volume reduction and deformation of the shape of the breast are the primary reasons for a poor cosmetic outcome. Such a breast deformity may be corrected by immediate transposition of adipose tissue with a vascular pedicle of latissimus dorsi muscle [21-23]. The location of the tumor is also a consideration. Patients with subareolar lesions have been found to have extensive spread of disease along the ducts that may not be excised with conservative resection [24]. Consequently, there is a high failure rate with BCT for these lesions [25]. However, such patients are acceptable candidates for BCT if resection involves removal of all or part of the nipple-areola complex in order to obtain tumor-free margins, and a reconstructive technique is employed [26].

## RISK FACTORS FOR LOCAL RECURRENCE

Local recurrence at any time leads to patient anxiety and may require salvage mastectomy [6]. Identification of patients at high risk for local recurrence should allow logical application of surgical and adjuvant treatment. Several studies have reported that no breast irradiation [15,27–30], positive surgical margins [31–35], extensive ductal carcinoma in situ (DCIS) [31,36–42], young age [15,31,38,42–47], multiple tumors [39,48], and high nuclear grade of tumor [28,39,42] are risk factors for local recurrences following BCT.

Extensive DCIS is the risk factor that has received the most attention [31,36–42]. Harris et al. [36] have reported the results of a retrospective clinicopathological review of 221 women with infiltrating ductal carcinoma who underwent local excision and radiation. The patients with extensive intraductal involvement had a 22% risk of local recurrence at 5 years, compared to only 1% for the remainder of patients. It has been suggested that extensive residual DCIS is the major contributor to local failure after conservative excision and radiotherapy, either because of the greater tumor burden, or to an inferior radiosensitivity of DCIS [49]. This high relapse rate is unacceptable, even though the presence of extensive intraductal component (EIC) does not influence survival [50]. In patients with extensive intraductal spreading carcinoma, total mastectomy or wide excision with microscopically tumor-free margins and radiation are reasonable options.

Several reports have suggested that very young patients are especially prone to local recurrence [15,31,38,42–47]. Since BCT is a particularly attractive alternative for the younger patient, the notion that this treatment approach might have serious disadvantages in this subgroup would have important consequences. However, the age dependence of both the intraductal component and lymphocytic stromal reaction has been reported [46,47,51]. Recht et al. [46] have reported extensive DCIS in 44% of patients younger than age 35, in 35% of those aged 35–50 years and in 27% of those older than age 50. Chabon et al. [51] have found a marked mononuclear cell reaction in 48% of patients aged 50 yrs or younger, compared with 23% of older patients. Kurtz et al. [39] have reported that the higher incidence of local failures observed in patients younger than 40 years of age reflects the greater prevalence of certain morphologic characteristics of the breast cancers in this age group, and that the age itself does not appear to be an independent determinant of risk. However, Boyages et al. [38] reported that EIC and very young age (defined as 34 years of age or younger) are independently associated with a high risk of breast recurrence for patients treated with limited excision prior to radiotherapy.

## MULTICENTRICITY OF BREAST CANCER AND EXTENT OF SURGICAL RESECTION

Although breast cancer is well recognized as a multicentric disease [52], it is important to distinguish between foci of cancer in direct relation to the main tumor (referred to as multifocality), and independent foci (referred to as multicentricity) [53]. Multifocal cancer in the vicinity of the tumor may consist of microscopic foci of an invasive tumor, emboli in lymphatic or vascular spaces, or, as is most frequently the case, intraductal carcinoma. True multicentricity in the breast is uncommon, whereas multifocality is frequent and can be extensive. In BCT, multifocal disease should be removed by partial mastectomy. Subclinical multicentric involvement can be eradicated by irradiation [54,55].

Partial mastectomy ranges from limited excision (or lumpectomy) with a grossly normal margin of tissue, to wide excision (or quadrantectomy), removing 2–4 cm of normal breast tissue around the tumor. However, these terms are not well defined. In 1990, a National Institutes of Health (NIH) Consensus Conference on the treatment of early-stage breast cancer determined that it is appropriate to excise the primary lesion with a normal tissue margin of appropriately 1 cm [1]. This recommendation presumes a grossly and microscopically uninvolved surgical margin. However, lumpectomy with grossly normal tissue margins will often leave residual microfoci of cancer cells. A recent study by Holland et al. [52] demonstrated a high incidence of multifocal disease left behind after partial mastectomy. In that study, if invasive tumors of <2-cm diameter had been removed with a surgical margin of 4 cm (quadrantectomy), 5% of those patients would have been found to have invasive tumor foci, and another 5% would have had noninvasive tumor foci elsewhere in the breast. However, if similar tumors had been removed with a 2-cm margin, the percentage of patients harboring invasive or noninvasive cancers elsewhere in the breast would have increased to 14% and 28%, respectively. These data indicate that quadrantectomy leaves less disease in the remaining breast than does wide excision with a 2-cm margin.

The radiation dose and extent of the surgery play a complementary role in the control of local disease. At the Institut Gustave Roussy, where a boost dose is used, locoregional recurrence was seen in 4 of 47 (9%) patients treated with quadrantectomy, compared with 20 of 389 (5%) patients treated with excisional biopsy [56]. Similarly, Chu et al. [57] did not find an advantage to quadrantectomy over excisional biopsy for patients treated with radiotherapy, including a boost to the primary site. However, quadrantectomy with total axillary dissection and radiotherapy (QUART) was compared to tumorectomy and axillary dissection followed by aggressive radiotherapy (TART) in a randomized trial conducted at the Milan Cancer Institute. Consequently, while no intergroup differences in the incidence of distant metastases and survival were observed, the TART patients had a much higher incidence of local recurrence (7.0 vs. 2.2%) [10]. Therefore, narrow margins of resection combined with aggressive irradiation is considered inadequate, and generous excision of normal tissue around the primary carcinoma is the treatment of choice. However, quadrantectomy sacrifice more normal tissue than is necessary for most patients. Unnecessarily wide margins should be avoided because the cosmetic outcome is related to the amount of tissue excised. The amount of breast tissue that must be excised in BCT needs to be individualized. For these reasons, a wide excision generally is preferable to a less complete excision (tumorectomy with no attention paid to margins) or a more radical excision (quadrantectomy) [58].

## SURGICAL MARGINS

Because of the multiple difficulties in assessing margin status accurately [59], there are no commonly accepted definitions of positive and negative margins. However, it has been accepted that positive surgical margins correlate with an increased risk of local recurrence [10,31,60,61], which usually occurs at the site of the previous surgery [10,62]. Lagios et al. [61] have reported that the risk of local recurrence among patients with microscopically involved resection margins was 73% (5/7), compared with 9% (2/23) in the patients with no tumor at the specimen edge. The risk of local recurrence would be diminished if a second, more extensive resection were performed at the initial operation to obtain tumor-free margins [63]. The best technique for examining the margin of the lumpectomy specimen may be inking of the surface for sectioning [64]. However, the suitability and practicality of techniques used to assess resection margins have been questioned [64] because they may underestimate the incidence of margin positivity [65,66]. Osteen et al. [49] recommended a stepwise approach to ensure the best cosmetic results and to minimize the risk of local recurrence. For T0 and small T1 lesions, gross tumor excision with a narrow rim of normal tissue can usually be performed under local anesthesia. By examination of permanent histologic sections, patients who have EIC can be identified for wider local excision. Macmillan et al. [65] recently reported cavity shaving and bed biopsy for assessment of surgical margins, and found a 38% incidence of tumor bed positivity following conventional lumpectomy. In their study, however, the total number of blocks for cavity shaving ranged between 20 and 40. This large number of blocks may render it impractical to evaluate the margin by frozen section during surgery. In our previous study [67], we have performed wide excision with 2 cm of normal breast tissue around the tumor. The periphery of the widely excised tissue was peeled like an orange and histologically examined on frozen and permanent section. If involved, the breast tissue adjacent to the primary site was also excised. Consequently, wide excision was performed without involved surgical margins in 89% of patients [68]. This method is more applicable to histologic assessment of the surgical margins after wide excision or quadrantectomy, than after tumorectomy or lumpectomy.

## IMPACT OF RADIATION ON LOCAL CONTROL

There is evidence that radiotherapy is effective in the control of microscopic residual disease, while the effectiveness of radiotherapy against gross residual tumor is limited. There are four randomized clinical trials comparing the outcome of conservative surgery alone to conservative surgery and radiotherapy for patients with early-

stage invasive breast cancer [12,27,28,69]. These prospective randomized trials show that the use of conservative surgery alone results in a much higher risk of local failure than the use of conservative surgery and radiotherapy, even when surgical resection margins are histologically uninvolved by tumor. Currently, however, there are many patients, particularly elderly ones, who are being treated with conservative surgery without radiotherapy [70,71]. It is clear that this approach is not as effective in preventing local recurrence as either mastectomy or conservative surgery and radiotherapy. On the basis of the available information, the Consensus Development Conference concluded that although local control can be obtained in some patients with local excision alone, no subgroups have been identified in which radiotherapy can be avoided [1]. However, there may be subsets of patients who might be treated adequately with surgery alone with acceptably low recurrence rates. Improved mammographic and pathological evaluation may identify patients with minimal or no multifocal involvement who can be treated without irradiation. Recently, Recht and Houihan [72] reviewed the available data regarding conservative surgery without radiotherapy and concluded that this remains an investigational approach.

## AXILLARY DISSECTION

The axilla may be managed with node sampling, partial or total dissection, and/or radiotherapy. Axillary node (AX) irradiation was not ineffective in the National Surgical Adjuvant Breast Project (NSABP) B-04 trial [73] but was of an inadequate dose in the Guy's Hospital trial [74]. However, this approach fails to provide information regarding AX status. AX dissection is commonly regarded as a reliable method of assessing nodal status and treating regional disease [75–77]. The number of involved nodes and extent of AX metastases are important prognostic factors that guide selection of those who might benefit from adjuvant treatment [78–80]. The incidence of progression of AX disease is unacceptably high when involved AX nodes are untreated [73,81,82]. However, routine AX dissection would expose a large percentage of patients with negative nodes to unnecessary perioperative risk and increased long-term morbidity [83–85]. There is considerable controversy concerning not only the indications for, but also the extent of AX dissection.

Most studies have shown that only 1–2% of patients with pathologically negative AX in levels 1 and 2 have metastases in level 3 [86,87]. By contrast, in the series reported by Rosen et al. [86], 22% of the patients with positive nodes in levels 1 or 2 had involvement of nodes at level 3. Similarly, in a previous study [87], we have reported that 23% of patients with positive nodes in levels 1 or 2 had involvement of nodes at level 3. Veronesi et al. [88] analyzed the distribution of AX metastases in 539 node-positive patients. The risk of metastases in the level 3 nodes was 42.9% if levels 1 and 2 were involved. If nodes were positive in level 1, levels 2 and/or 3 were involved in 41% of cases. These data indicate that a partial (level 1–2) dissection is adequate in patients with negative AX, but a total (level 1–3) AX dissection is necessary in those with positive AX. Kinne [58] recommended that a partial dissection be performed in patients with clinically negative nodes. In the patients with clinically involved nodes, a total dissection is recommended, to avoid subsequent irradiation of the axilla.

However, clinical assessment of disease of the AX lymph nodes is associated with a significant incidence of error [73,89,90]. In an effort to assess AX nodal status intraoperatively, several investigators have performed AX sampling or biopsy with cytologic or histologic examination [91–98]. However, a significant number of patients with involved AX are not identified using this approach. Moreover, AX sampling may not provide accurate information regarding the number of AX nodes involved. In a previous study [98], we have shown that AX sampling fails to detect the presence of metastases in 19 of 84 (23%) patients with AX involvement. In order to avoid unnecessary AX dissection, it will be necessary to develop a new method of assessing AX involvement more accurately before or during surgery. Recently, however, a sentinel node biopsy has been proposed for identifying AX metastases [99,100]. Giuliano et al. [99] reported that a sentinel lymph node was detected in 114 of 173 (66%) procedures, and it accurately identified AX nodal status in 109 of 114 (96%). While this technique is still investigational [100], it is a potentially useful way of assessing AX nodal status and obviating AX dissection in node-negative patients.

Ductal carcinoma in situ (DCIS) has limited potential for metastatic spread to AX nodes [101,102]. Silverstein et al. [101] have reported that of 100 patients with DCIS, none had positive AX lymph nodes. However, Lagios et al. [103] reported that of 24 DCIS lesions ≥26 mm, 11 (46%) demonstrated occult foci of invasion and 1 had nodal metastases. Moreover, Carter and Smith [104] reported that of 29 patients with biopsy-proven DCIS who underwent mastectomy and AX dissection, 4 (14%) had positive nodes (3 patients with invasive duct carcinoma and 1 with DCIS). Therefore, AX dissection is unnecessary for most small intraductal tumor [101,102], but AX metastases must be considered in patients with larger tumors, multicentric tumors, and tumors with microinvasion [103,104].

Recently, clinicians have become less dependent on histologic AX status for decision making in patients with breast cancer [105]. Because of the widespread use of adjuvant systemic therapy, even if the AX nodes are histologically negative, the role of AX dissection is being questioned. Recently, many biologic factors, such as DNA ploidy, c-*erb*B-2 expression, epidermal growth factor re-

ceptor (EGFR) expression, and p53 alteration, have been proposed, but their value as prognostic indicators remains controversial [106]. At present, the decision-making process for adjuvant systemic therapy still largely depends on histologic AX nodal status [107]. Therefore, a partial or total AX dissection should be performed to provide prognostic information and treat regional disease until an alternative to AX dissection is found. As an exception, AX dissection may be avoided for most intraductal or very small invasive carcinomas [101,102].

## CONCLUSIONS

1. Patient selection is important, as not all patients benefit from BCT. The criteria for patient selection are resection of the primary tumor without causing major cosmetic deformities and minimizing the likelihood of local recurrence.
2. A wide excision is preferable to a less complete excision (tumorectomy) or a more radical excision (quadrantectomy).
3. Accurate assessment of the surgical margins is important. The risk of local recurrence may be diminished if a second resection is performed to obtain tumor-free margins. However, the suitability and practicality of techniques used to assess resection margins have been questioned.
4. Radiotherapy is an integral part of BCT. Surgery alone remains an investigational approach.
5. AX dissection is commonly regarded as a reliable method of assessing nodal status and treating regional disease. AX dissection may be avoided for most intraductal or very small invasive carcinoma because of the limited potential for metastatic spread to the AX nodes.

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